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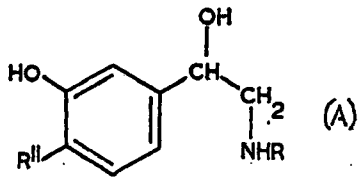
(54) HETEROCYCLIC DERIVATIVES OF GLYOXYLIC ACID, PROCESS FOR THEIR PREPARATION AND THERAPEUTICAL COMPOSITION CONTAINING SAME

(71) We, LABORATOIRES HOUDE, a French Body Corporate, residing at 15, Rue Olivier-Métra, 75 Paris, France, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

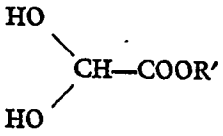
This invention relates to heterocyclic derivatives of glyoxylic acid having useful pharmacological properties, to a process for the preparation of such products and to a therapeutic composition containing said derivatives.

The new products of the invention consist of the reaction products of one mole of a compound of formula:



(A)

with one mole of a compound of formula:

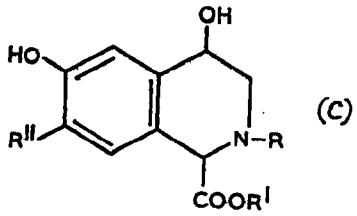


(B)

in which formula R and R', which may be the same or different, represent hydrogen or a lower alkyl group of 1—8 carbon atoms and R'' is hydrogen or a hydroxy group.

According to the compounds (A) and (B) used, the reaction product is:

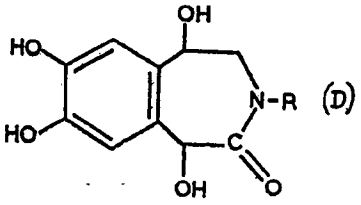
a) either a compound of formula:



(C)

or a compound of equimolar quantities of the *cis* and *trans* forms of this compound (hereinafter referred to as a "mutual salt", when R'=H;

b) or a compound of formula:



(D)

in the case where, in starting compounds (A) and (B), R'=H and R''=OH;

c) or a mixture of the compounds defined under a) and b) above.

For example when, in starting compound (A), R'' is hydrogen, the reaction product is essentially a compound of formula (C), or a mutual salt when R'=H; when, in the starting compounds, R=H or iso. C_3H_7, R'=H and R''=OH, the reaction product is essentially a compound of formula (D); in other cases, there is obtained a mixture of the compounds defined under a) and b) above, and particularly in the case where R=CH_3; R'=H and R'=OH there is obtained a mixture

[*Price 25p*]

of the mutual salt of the *cis* and *trans* forms of compound of formula (C) and of compound of formula (D).

All compounds or mixtures defined under a), b) and c) above exhibit, to varying degrees, an antitussive activity useful in human therapeutics and a very low toxicity.

The invention relates also to a process for the preparation of products derived from glyoxylic acid, comprising reacting a compound of formula A with a compound of formula B, wherein R, R′ and R″ have the above defined meanings, and collecting the resulting reaction product.

The reaction between compound (A) and glyoxylic acid or its ester of formula (B) is generally carried out at room temperature, the glyoxylic acid or its ester preferably being added in equimolecular amount, in aqueous or alcoholic solution (sometimes slightly acidified when a glyoxylic acid ester is used) to arylethanolamine (A).

Dissolution is made complete by stirring; heat is generally evolved, which is limited by cooling under a stream of water, together with a slight discoloration of the solution. The reaction product crystallizes spontaneously; it is then suction filtered and recrystallized from water or an organic solvent, according to the case. The esters of formula (C) may also be prepared by esterification of acids of formula (C) with the corresponding alcohols R′OH, in the presence of anhydrous hydrochloric acid.

The following non-limiting examples are given to illustrate the invention.

Example 1

1) Mutual salt of *cis* and *trans* - 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline 1 - carboxylic acids (I) (R=CH_3; R′=R″=H).

To a conical flask containing 16.76 g (0.1 mole) of a powdered phenylephrine base is added an aqueous solution of 9.2 g (0.1 mole) of glyoxylic acid monohydrate. The mixture is stirred until completely dissolved; heat is evolved. Crystallization is promoted by scratching, the reaction is cooled under a stream of water and crystallization is completed in the refrigerator. The crystalline material is suction filtered, washed with cold water (2×20 ml), and then with alcohol and with ether and is then dried in air to constant weight, to give 16.5 g (yield: 73%) of pure product melting at 230—235°C with decomposition.

Analysis

	C%	H%	N%
Calculated for $C_{11}H_{13}NO_4$:	59.19	5.87	6.25
Found	59.21	5.78	6.45

2) *cis* - 4,6 - Dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline 1 - carboxylic acid (Ia) (Formula C)

a) 0.076 mole of the methyl ester of 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline 1 - carboxylic acid, prepared as in example 4 hereinunder, is heated with 45 ml of 2N sodium hydroxide under refluxing conditions; the precipitate is suction filtered and is then suspended in a few ml of water; the pH is brought to 5—6 with 6N HCl; the material is again suction filtered; it is then washed twice with 15 ml of cooled water, and then with alcohol and with ether. The product is obtained with a yield of 57%, m.p.=225°C with dec. Concentrating the mother-liquors to dryness and taking up the crystalline residue into 18 ml of boiling water makes it possible to collect 1 g of product, which brings the yield up to 63%.

b) The product may also be obtained by methylation of the N - unsubstituted acid (see Example 2). 55 g (0.06 mole) of product of example 2, 13. 8 g (0.3 mole) of formic acid and 18 g (0.18 mole) of 30% formalin are refluxed, using a water-bath, during 8 hours. The mixture is taken up into water and neutralized, which causes crystallization of a material entirely identical with that described above under a).

3) *Trans* - 4,6 - Dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - iso - quinoline 1 - carboxylic acid (Ib) (Formula C)

Glyoxylic acid monohydrate (0.036 mole) is dissolved in 112 ml of dimethylsulfoxide; phenylephine base (0.036 mole) is added thereto, with stirring; the temperature rises then to about 45°C and complete dissolution is obtained, followed by precipitation. Stirring is contained for a further 4 hours, the precipitate is suction filtered through sintered glass and is then washed with dimethylsulfoxide (20 ml) and then with alcohol and with ether. There are recovered 45 g of compound (I) with a yield of 56%. When 400 ml of absolute ethanol and 200 ml of ether are added to the combined filtrates, a gummy mass which crystallizes is produced. This is suction filtered and then washed with alcohol and with ether; thus is isolated *trans* isomer (Ib) with a yield of 27.8% (22.3 g), m.p. 224—225°C (dec.). When equal parts of (Ia) and (Ib) are dissolved in boiling water, product (I) crystallizes on cooling.

Example 2

Mutual salt of *cis* and *trans* - 4,6 - dihydroxy - 1,2,3,4 - tetrahydro - isoquinoline 1 - carboxylic acid (II) (R′=R″=H).

The procedure of Example 1, 1), is used, substituting 0.1 mole of phenylephrine with 0.1 mole of norphenylephrine. Yield: 87.4%; m.p.=238°C.

Analysis
Calculated for $C_{10}H_{11}NO_4$

	C%	H%	N%
	57.42	5.30	6.69
Found			
	57.53	5.02	6.68

EXAMPLE 3

Mutual salt of *cis* and *trans* - 4,6 - dihydroxy - 2 - ethyl - 1,2,3,4 - tetrahydro - isoquinoline 1 - carboxylic acids (III) ($R=C_2H_5$; $R'=R''=H$)

The procedure of Example 1, 1), is used, substituting 0.1 mole of phenylephrine with 0.1 mole of N - ethyl - norphenylephrine and substituting the water with ethanol to dissolve the glyoxylic acid. Yield: 80%; m.p. 212°C.

Analysis
Calculated for $C_{12}H_{15}NO_4$

	C%	H%	N%
	60.75	6.37	5.90
Found			
	60.30	6.61	5.75

EXAMPLE 4

Methyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (IV) ($R=CH_3$; $R'=CH_3$; $R''=H$)

a) Direct condensation from methyl glyoxylate

Phenylephrine (5 g; 0.025 mole) is heated in 10 ml of methanol; methyl glyoxylate (2.15 g; 0.025 mole) is cautiously added to the hot solution; if required, the pH is acidified to a value of 2, with hydrochloric acid; the contacting is allowed to continue at least during 2 days; the solution is concentrated *in vacuo*, over a water-bath, the solvent is completely removed, the viscous residue is dissolved in the minimum amount of water (made alkaline to pH 8—9 with ammonia), to give a precipitate which is suction filtered, washed with water and dried. m.p. 159—160°; Weight: 2.35 g (yield: 40%)

b) Esterification of the corresponding acid:

40 g of Compound (I) of Example 1 dissolved in methanol (400 ml) containing dry hydrochloric acid (40 g) are refluxed during 2 hours; the solution is concentrated to dryness *in vacuo*, over the water-bath, the residue is taken up into a mixture of methanol and benzene; it is then again concentrated to dryness, and the procedure is repeated a number of times to dry the material completely. The residue is taken up into 400 ml of methanol containing 40 g of dry hydrochloric acid and is then refluxed during 2 hours. These operations are repeated three times, final evaporation to dryness is then carried out and the residue is finally dissolved in water (60 ml) containing ammonia (200 ml) at 20° Bé. Crystallization occurs spontaneously; the crystalline product is suction filtered, washed with water and dried.

— 1st crop: m.p. 159—160°C. Weight: 18.59 g
— 2nd crop (which separates from the filtrate): m.p. 158—160°C, weight: 14.91 g.
Total weight: 33.5 g, i.e., a yield of 75.5%

The products obtained under a) and b) are identical.

Analysis
Calculated for $C_{12}H_{15}NO_4$

	C%	H%	N%
	60.76	6.33	6.91
Found			
	60.43	6.39	6.01

EXAMPLE 5

Ethyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (V) ($R=CH_3$; $R'=C_2H_5$; $R''=H$) (Formula C)

a) Direct condensation from ethyl glyoxylate

The procedure of Example 4 a) is used, substituting 0.025 mole of methyl glyoxylate with 0.025 mole of ethyl glyoxylate. m.p.=159—160°. Recrystallized from water, m.p. 168°. Yield. 40%.

b Esterification

The procedure of Example 4 b) is used, substituting the methanol ic hydrochloric acid solution with ethanol (400 ml) containing dry hydrochloric acid (40 g). The material is suction filtered, washed with water and dried to give the ethyl ester with a yield of 65%. m.p.=170°C.

Analysis
Calculated for $C_{13}H_{17}NO_4$

	C%	H%	N%
	62.14	6.82	5.57
Found			
	62.35	7.04	5.62

Products a) and b) are identical.

EXAMPLE 6

Propyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (VI) ($R=CH_3$; $R'=C_3H_7$; $R''=H$) (Formula C)

a) Direct condensation from propyl glyoxylate

The procedure of Example 4 a) is used, substituting the methyl glyoxylate with 0.025 mole of propyl glyoxylate. This gives a product melting at 157°S after recrystallization from acetone and, from a 2nd crop, the mix-

ture of *cis* (VIa) and *trans* (VIb) is obtained (Yield: 20%; m.p. 140°).

b) Esterification

The procedure of Example 4 b) is used, substituting the methanol ic hydrochloric acid solution with propanol (400 ml) containing dry hydrochloric acid (40 g); this gives a product which, in recrystallization from acetone, melts at 157°C. Yield: 97%.

Analysis

Calculated for $C_{14}H_{19}NO_4$

	C%	H%	N%
	63.38	7.22	5.28
Found	63.62	7.22	5.44

Example 7

Isopropyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (VII) (R=CH_3; R'= iso. C_3H_7; R''=H) (Formula C)

a) Condensation from isopropyl glyoxylate

The procedure of Example 4a) is used, substituting 0.025 mole of methyl glyoxylate with 0.025 mole of isopropyl glyoxylate. Recrystallization is carried out from methanol. There are obtained a 1st crop, m.p. 170°C (Yield: 31%) followed by a 2nd crop, m.p. 165°C (yield: 16%) containing both the *cis* and *trans* isomers.

b) Esterification

The procedure of Example 4 b) is used, substituting the methanol ic hydrochloric acid solution with isopropanol (400 ml) containing dry hydrochloric acid (40 g). A product melting at 168—170°C is obtained. Yield: 50%

Analysis

Calculated for $C_{14}H_{19}NO_4$

	C%	H%	N%
	63.38	7.22	5.28
Found	63.32	7.43	5.30

Example 8

Butyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (VIII) (R=CH_3; R'=C_4H_9; R''=H) (Formula C)

a) Condensation from butyl glyoxylate

The procedure of Example 4 a) is used, substituting 0.025 mole of methyl glyoxylate with 0.025 mole of butyl glyoxylate. A first crop (yield: 89%) is obtained which, on recrystallization from methanol, melts at 143—145°C, followed by a 2nd crop containing both the *cis* and *trans* isomers, with a yield of 12%, m.p. about 128°C.

b) Esterification

The procedure of Example 4 b) is used, substituting the methanol ic hydrochloric acid solution with butanol (400 ml) containing dry hydrochloric acid (40 g). A product melting at 143—145°C is obtained.

Analysis

Calculated for $C_{15}H_{21}NO_4$

	C%	H%	N%
	64.49	7.58	5.01
Found	64.59	7.57	5.20

Example 9

Isobutyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (IX) (R=CH_3; R'=iso.C_4H_9; R''=H) (Formula C)

a) Condensation from isobutyl glyoxylate

The procedure of Example 4 a) is used, substituting the methyl glyoxylate with 0.025 mole of isobutyl glyoxylate. A first crop (Yield 40%), m.p. 166—168°C is obtained, and then a second crop, m.p. about 150°C (Yield: 10%) which is the mixture of the *cis* and *trans* isomers.

b) Esterification

The procedure of Example 4 b) is used, substituting the methanol ic hydrochloric acid solution with isobutanol (400 ml) containing dry hydrochloric acid (40 g). A product melting at 165°C is obtained. Yield: 82%.

Analysis

Calculated for $C_{15}H_{21}NO_4$

	C%	H%	N%
	64.49	7.58	5.01
Found	64.20	7.78	5.06

Example 10

Amyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (X) (R=CH_3; R'=C_5H_{11}; R''=H (Formula C)

a) Condensation from amyl glyoxylate

The procedure of Example 4 a) is used, substituting the methyl glyoxylate with 0.025 mole of amyl glyoxylate. A product melting at 130°C after recrystallization from aqueous methanol is obtained (Yield: 27%).

b) Esterification

The procedure of Example 4 a) is used, substituting the methanol ic hydrochloric acid solution with amyl alcohol (400 ml) containing dry hydrochloric acid (40 g). This gives, with a yield of 26.5%, a product which melts at 130°C on recrystallization from aqueous methanol.

Analysis
Calculated for $C_{16}H_{23}NO_4$

	C%	H%	N%
	65.51	7.90	4.28
Found			
	65.69	8.04	4.88

EXAMPLE 11

Isoamyl 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (XI) (R=CH_3; R'=iso.C_5H_{11}; R''=H) (Formula C)

a) Condensation from isoamyl glyoxylate

The procedure of Example 4 a) is used, substituting the methyl glyoxylate with 0.025 mole of isoamyl glyoxylate. Yield: 40%; m.p. 153—155°C; the product may be recrystallized from aqueous methanol.

b) Esterification

The procedure of Example 4 b) is used, substituting the methanol ic hydrochloric acid solution with isoamyl alcohol (400 ml) containing dry hydrochloric acid (40 g). A product which, on recrystallization from aqueous methanol, melts at 153—155° (Yield 19%) is thereby obtained.

Analysis
Calculated for $C_{16}H_{23}NO_4$

	C%	H%	N%
	65.51	7.90	4.78
Found			
	65.38	7.94	4.82

EXAMPLE 12

Methyl 4,6 - dihydroxy - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (XII) (R=H; R'=CH_3; R''=T) (Formula C)

The procedure of Example 4 b) is used, substituting the 40 g of compound (I) with 40 g of compound (II) of Example 2; on recrystallization from aqueous methanol, a product melting at 180°C (with decomposition) is obtained (Yield: 65%).

Analysis
Calculated for $C_{11}H_{13}NO_4$

	C%	H%
	59.18	5.87
Found		
	59.11	5.68

EXAMPLE 13

Ethyl 4,6 - dihydroxy - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (XIII) (R=H; R'=C_2H_5; R''=H) (Formula C)

The procedure of Example 5 b) is used, substituting compound (I) with compound (II); recrystallization from methanol gives a first crop which is a mixture of both *cis* and *trans* isomers, melting at 180—190°C (Yield: 66,4%) and a second crop melting at 194—195° corresponding to one of the isomers in pure form.

Analysis
Calculated for $C_{12}H_{15}NO_4$

	C%	H%	N%
	60.75	6.37	5.90
Found			
	60.69	6.48	6.05

EXAMPLE 14

Propyl 4,6 - dihydroxy - 1,2,3,4 - isoquinoline carboxylate (XIV) (R=H; R'=C_3H_7; R''=H) (Formula C)

The procedure of Example 6 b) is used, substituting compound (I) with compound (II). On recrystallization from 50% aqueous methanol, the product melts at 165—166° (Yields=52%).

Analysis
Calculated for $C_{13}H_{17}NO_4$

	C%	H%	N%
	62.14	6.82	5.57
Found			
	61.97	6.75	5.58

EXAMPLE 15

Isobutyl 4,6 - dihydroxy - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (XV) (R=H; R'=iso.C_4H_9; R''=H) (Formula C)

The procedure of Example 9 b) is used, substituting compound (I) with compound (II). On recrystallization from methylethyl ketone, the product melts at 148—149°C (Yield: 14%3

Analysis
Calculated for $C_{14}H_{19}NO_4$

	C%	H%	N%
	63.38	7.22	5.28
Found			
	63.19	7.23	5.27

EXAMPLE 16

Isoamyl 4,6 - dihydroxy - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (XVI) (R=H; R'=iso.C_5H_{11}; R''=H) (Formula C)

The procedure of Example 11 b) is used, substituting compound (I) with compound (II). The resulting product is recrystallized from methylethylketone (Yield 10%).

Analysis
Calculated for $C_{15}H_{21}NO_4 \cdot H_2O$ (3/4)

	C%	H%	N%
	61.52	7.74	4.48
Found			
	61.49	7.49	4.78

EXAMPLE 17

Methyl 4,6 - dihydroxy - 2 - ethyl - 1,2,3,4 - tetrahydro - isoquinoline carboxylate (XVII) ($R=C_2H_5$; $R'=CH_3$; $R''=H$) (Formula C)

The procedure of Example 4 b) is used, substituting the 40 g of compound (I) with 40 g of compound (III) of Example 4. Yield: 65%, m.p. 139—140°

Analysis

Calculated for $C_{12}H_{17}NO_4$	C%	H%	N%
	62.13	6.82	5.57
Found	62.13	6.91	5.67

EXAMPLE 18

Mixture of the mutual salts of *cis* and *trans* - 4,6,7 - trihydroxy - 2 - methyl - 1,2,3,4 - tetrahydro - isoquinoline 1 - carboxylic acids (XVIII) $R=CH_3$; $R'=H$; $R''=OH$) and of 1,5,7,8 - tetrahydroxy - 3 - methyl - 2,3,4,5 - tetrahydro - 3 - (1H) - benzazepin - 2 - one (XIX) ($R=CH_3$; formula D).

An aqueous solution of glyoxylic acid monohydrate (0.03 mole) is poured over powdered adrenalin base (0.03 mole); the mixture is thoroughly stirred and the whole solubilizes, after which the solution becomes discolored and crystallizes spontaneously. The precipitate is suction filtered, washed with alcohol and with ether, and is then dried in air to constant weight. Yield: 93%. m.p. 180°C with decomposition.

Analysis

Calculated for $C_{11}H_{13}NO_5 \cdot H_2O$	C%	H%	N%
	51.36	5.87	5.44
Found	51.69	5.62	5.64

EXAMPLE 19

1,5,7,8 - Tetrahydroxy - 3 - methyl - 2,3,4,5 - tetrahydro - 3(1H) - benzazepin - 2 - one (XIX) ($R=SH_3$; formula D)

5 g of the product prepared in Example 18 (mixture XVIII+XIX) are contacted in the cold with 10 ml of N HCl during 24 hours after which an insoluble portion is found to remain. The latter is suction filtered and then washed with alcohol and with ether. This insoluble fraction (1.3 g) constitutes the pure product (XIX); m.p. 185—188°; Yield: 26%

Analysis

Calculated for $C_{11}H_{13}NO_5$	C%	H%	N%
	55.23	5.48	5.86
Found	55.11	5.37	5.71

EXAMPLE 20

1,5,7,8 - Tetrahydroxy - 2,3,4,5 - tetrahydro - 3 - (1H) - benzazepin - 2 - one (XX) (R=H; formula D).

An aqueous solution of glyoxylic acid monohydrate (6 g; 0.066 mole) in water (10 ml) is poured over 0.06 mole of noradrenalin base. The mixtures becomes discolored and warms up slightly; scratching the walls of the container with a rod produces a crystalline material which is suction filtered, washed with water, with alcohol and finally with ether. This is dried in air to constant weight to give 12 g (Yield: 80%) of product melting at 205°C, containing one mole of water.

Analysis

Calculated for $C_{10}H_{11}NO_5 \cdot H_2O$	C%	H%	N%
	49.38	5.39	5.76
Found	49.42	5.40	5.87

EXAMPLE 21

1,5,7,8 - Tetrahydroxy - 2 - isopropyl - 2,3,4,5 - tetrahydro - 3 - (1H) - benzazepin - 2 - one (XXI) ($R=iso.C_5H_7$; Formula D)

An aqueous solution of glyoxylic acid monohydrate (1 g; 0.011 mole) is poured over isoprenalin base (2 g; 0.01 mole). The mixture becomes discolored and warms up slightly; scratching the walls with a rod gives a crystalline material which is suction filtered, washed with water, then with alcohol and finally with ether, and is then dried in air to constant weight. Yield: 82%; m.p. 188—190°C.

Analysis

Calculated for $C_{12}H_{17}NO_5$	C%	H%	N%	O%
	58.42	6.41	5.24	29.93
Found	58.53	6.53		30.03

Results of toxicological and pharmacological test carried out with some of the products according to the invention, and particularly those of the preceding examples (the reference numbers of the products are given in said examples) will now be given for illustrative purposes.

I, Acute toxicity
LD_{50} in mice, mg/kg

Product No.	Route of administration: intra-venous	intra-peritoneal	per os
I	> 800	>1000	>1000
Ia	>1000	>1000	>1000
Ib	> 800	>1000	>1000
II	—	> 600	>1000
III	> 800	>1000	>1000
IV	250	500	>1000
VI	300	600	1000
Mixture VIa+VIb	350	600	1000
VIII	160	450	800
IX	180	>1000	>1000
XI	150	>1000	>1000
XIII	650	>1000	>1000
XV	420	> 600	1000
Mixture XVIII+XIX (Ex. 18)	>1500	>1500	>1500
XX	> 500	>1000	>1000
Codein phosphate (for comparative purposes)	65	130	—

Thus, it is apparent that the acute toxicity of all products tested is extremely low and always much lower than of codein phosphate.

II. Systemic effects

At dosages of 2—20 mg/kg, by the intravenous route in rat, guinea-pig or rabbit, the only effects found for some of the products are a low and transient hypotension and a respiratory stimulation, also of short duration. Only the two o-diphenolic materials tested (mixture XVIII+XIX and compound XX) induce a transient hypertension at strong dosages (dosage about 1000 to 2000 times that of adrenalin and of noradrenalin to produce the same effect).

III. Anti-tussive activity

1) Products (I), (Ia) and (III) protect markedly the quinea-pig against coughing induced by ammonia aerosols, according to the technique of C. A. Winter and L. Flataker (J. Pharmacol, exper. Therap., 1954, 112, 99).

2) Product (I) was compared with codein phosphate in decerebrated guinea-pig, coughing being induced by touching the inner tracheal walls with a small catheter, according to M. Lemeignan, G. Streichenberger & P. Lechat (Thérapie, 21, 361)

In administration by the intra-peritoneal route, 60 mg/kg of (I) and 10 mg/kg of codein phosphate have a comparable activity, decreasing strongly the severity of the coughing fits during 40—60 minutes (5 mg/kg of codein phosphate are inactive). It should be noted that (I) is free from any toxicity by the intra-peritoneal route (LD_{50} above 1 g/kg) whereas that of codein phosphate, by this route, is 130 mg/kg.

3) Product (I) and its constituents (Ia) and (Ib), and also products (X), (XIII) and (XX) were submitted to R. Domenjoz's test (Arch. Exp. Pathol. Pharmacol., 1952, 215, 19) which comprises stimulating electrically the upper laryngeal nerve in cat while the trachae is connected through a cannula with a Marey drum which records the respiration and its variations under the influence of coughing. Codein phosphate was used as reference material.

(I) and (Ib) have an anti-tussive activity that is comparable in intensity to that of codein phosphate at the same dosages. The activity of (Ia) is markedly lower. Duration of the action of (I) is comparable to that of codein phosphate and higher than that of (Ia) and (Ib) administered separately.

The anti-tussive activity of (XIII) is close to that of (I) both with respect to intensity and to duration, that of (X) is close, as to intensity, but lower as to duration, and that of (XX) is marked, but lower than that of (I) with respect to intensity.

IV. Action on intestinal transit

Product (I) has no action on intestinal transit in mice, whereas codein phosphate slows it down strongly: after administration of a charcoal slurry to three lots of 10 mice, the average percentages of the length of intestine travelled by the charcoal are the following:

Reference animals: 59.7%	
Treated with 75 mg/kg codein phosphate *per os*	13.2%
Treated with 150 mg/kg of product (I) per *os*	60.7%

V. To *conclude*, the products according to the invention, and more particularly product (I), mutual salt of *cis*- and *trans* - 4,6 - dihydroxy - 1,2,3,4 - tetrahydro - isoquinaldic acids, are endowed with anti-tussive properties equivalent to those of codein, with the follow-

ing advantages over the latter: acute toxicity practically nil, absence of paralysing action on the intestine and absence of respiratory depressant action.

They are applicable in human therapeutics for the treatment of coughing from any origin: tracheitis, rhinopharyngitis, laryngitis, bronchitis, acute and chronic pneumonopathy, influenza, spasmodic and reflex coughing, coughing fits, whooping-cough, turberculosis.

Therefore, the present invention relates also to a therapeutic composition containing, as active principle, a reaction product as defined previously together with a pharmaceutically acceptable vehicle.

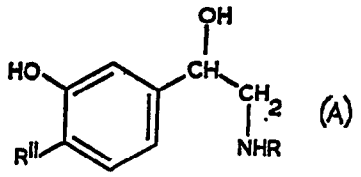
The composition of the invention is administrable by the oral or rectal route, for example at a daily dosage regimen of 0.05—1 g, or more, of active principle, according to the case.

For administration, the composition is formulated in particular as tablets, coated tablets or capsules, containing for example 25—250 mg of active ingredient per unit dose, or as sweetened and flavored granules or suspensions containing 0.5—5%, by weight, of active ingredient, or also in the form of suppositories containing each 50—500 mg of active ingredient.

In such pharmaceutical forms, the active ingredient is associated with the suitable well-known vehicles or excipients.

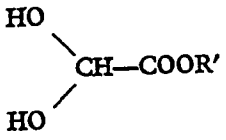
WHAT WE CLAIM IS:—

1. A reaction product of one mole of an arylethanolamine of formula



(A)

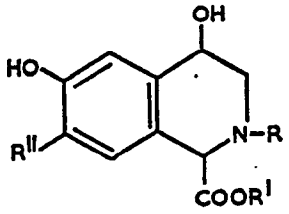
with one or more of a glycolic acid or ester thereof of formula



(B)

in which R and R', which may be the same or different, represent hydrogen or an alkyl group having from 1 to 8 carbon atoms and R'' is hydrogen or a hydroxy group.

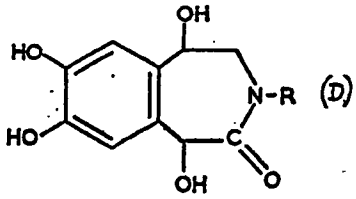
2. A compound of formula



(C)

in which R, R' and R'' have the same meanings as in claim 1, or a compound of equimolar quantities of the *cis* and *trans* forms of said compound (C) when R' is hydrogen.

3. A compound of formula



(D)

in which R has the same meaning as in claim 1.

4. A mixture of a compound according to claim 2 and a compound according to claim 3.

5. A compound of equimolar quantities of *cis*- and *trans* - 4,6 - dihydroxy - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline 1 - carboxylic acids.

6. A process for the production of a compounds of formula (C), as hereinbefore defined, and/or a compound of equimolar quantities of the *cis* and *trans* forms of said compound (C), where R' is hydrogen, and/or of formula (D), as hereinbefore defined, which process comprises reacting an arylethanolamine of formula (A), as hereinbefore defined, with a glyoxylic acid or ester thereof of formula (B), as hereinbefore defined.

7. A process according to claim 6, in which said glyoxylic acid or ester thereof is used in aqueous or alcoholic solution.

8. A process according to claim 6, substantially as hereinbefore described with reference to any one of the foregoing Examples.

9. A compound of formula (C) or a compound of equimolar quantities of the *cis* and trans forms of said compound (C) when produced by a process according to any one of claims 6 to 8.

10. A compound of formula (D) when pro-

duced by a process according to any one of claims 6 to 8.

11. A therapeutic composition comprising a compound according to any of claims 2, 3, 9 or 10 and a pharmaceutically acceptable vehicle.

12. A composition according to claim 11, in unit dosage form.

13. A composition according to claim 12, suitable for oral administration, in which each unit dose contains from 25 to 250 mg of said compound.

14. A composition according to claim 13, in the form of a tablet, a coated tablet or a capsule.

15. A composition according to claim 12, in the form of a suppository containing 50 to 500 mg of said compound.

16. A composition according to claim 11, in the form of sweetened and flavoured granules or suspension containing from 0.5 to 5 per cent by weight of said compound.

17. A therapeutic composition according to claim 11, substantially as hereinbefore described.

MARKS & CLERK.

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ENGLISH ABSTRACT FOR SU1238732

1 / 1 WPAT - ©The Thomson Corp.

Derwent Accession :
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Title :
Alpha-2 antagonist compsn. contg. 3-benzazepine cpd. esp. for reducing intra=ocular pressure and blood pressure

Derwent Class :
B02

Patent Assignee :
(SMIK) SMITHKLINE BECKMAN CORP

Inventor :
DEMARINIS RM; HIEBLE JP; MATTHEWS WD

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Abstract :
EP--80779 A
An alpha-2 antagonist compsn. comprises a carrier and a 3-benzazepine cpd. of formula (I) or its pharmaceutically acceptable acid addn. salt. (R is 1-3C alkyl or allyl. X is halo). Most pref. (I) is 6-chloro -2,3,4,5-tetrahydro-3-methyl-1H-benzazepine (Ia) used as its hydrochloride salt. Esp. (I) are used to reduce intraocular pressure (treatment of glaucoma); as cardiovascular agents (treatment of congestive heart failure, angina pectoris and thrombosis) and as antihypertensives. They have no direct effect on pupil size and no effect on heart rate or blood pressure in normotensive subjects.

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